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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,725	07/15/2003	Gregory M. Lanza	532512000401	1157

25225 7590 05/18/2007
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EXAMINER	
BARHAM, BETHANY P	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
05/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/620,725	LANZA ET AL.	
	Examiner	Art Unit	
	Bethany P. Barham	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-79 and 82-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-79 and 82-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt is acknowledged of the Applicant's Amended Claims, Remarks, and 132 Declaration filed on 10/31/2006. It should be noted that this application has been transferred from Examiner David Vanik to Bethany Barham.

The 35 U.S.C. 102 rejections over US 5,690,907, US 5,780,010, or US 5,958,371 by themselves or in combination with US 5,656,287 ('287) and the 102/103 over 2001/0018072 are hereby maintained.

Response to 132 Declaration

The declaration under 37 CFR 1.132 filed 10/31/2006 is insufficient to overcome the rejection of claims 71-79 and 82-93 based upon the 102/103 over 2001/0018072 ('072) as set forth in the last Office action because: '072 teaches the same core fluorocarbon (such as perfluorooctylbromide) and lipid bilayer, since the fluorocarbon disclosed is the same as that used by applicant in Example 1 it is therefore a liquid. Secondly, the declaration does not demonstrate that the drug itself is present on the outside of the particle, but rather that the ingredients are mixed together and it is well known in the art that a lipophilic drug will be held in a hydrophobic core and in the lipid lipophilic bilayer.

MAINTAINED REJECTIONS

The following are maintained rejections:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 71-79 and 82-86 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,690,907, US 5,780,010, or US 5,958,371 as evidenced by US 4,595,680, US 5,656,287, or US 6,149,937.

- Lanza in these patents discloses a method of delivery of an active agent to the target site using the same emulsions. The emulsions are oil-in-water emulsions containing a ligand (avidin, antibodies), an active agent, and perfluorococtytbromide. The particles are coated with a lipid/surfactant. The lipids include phospholipids such as phosphatidylcholine, fatty acids (anionic) and stearylamine (cationic). It should be noted that applicant views

phosphatidylcholine (1,2 diacyl-snoglycerol-3-ethylphosphocholine) as a cationic lipid (see original canceled claim 15).

- The particles are of instant sizes (note the abstract, col. 4, line10 through col. 6, line 46, Col. 7, line 48 et seq,, Examples and claims of 907; col. 4, line 25 through col. 8, line 9, Examples and claims of 010 and 371).
- As set forth in US 5,690,907, biotinylated phosphatidylethanolamine is incorporated into the outer lipid monolayer of the perfluorocarbon emulsion nanoparticles (Example 2; column 8, lines 66-67). As evidenced by US 4,595,680, phosphatidylethanolamine can be considered to be a drug, having activity against disorders related to the central nervous system (abstract). Thus, US 5,690,907 explicitly teaches the incorporation of a drug, phosphatidylethanolamine, into the outer lipid layer of a perfluorocarbon emulsion nanoparticle. Additionally, US 5,690,907 also disclose combining the ligand-based perfluorocarbon emulsion nanoparticle system with chemotherapeutic agents or other drugs (column 7, lines 48-67).
- A specific example of the drugs set forth by US 5,690,907 is doxorubicin (column 7, line 54). Doxorubicin is a lipophilic drug that would have a tendency to incorporate into a lipid layer of a nanoparticle (See US 5,656,287 - column 2, lines 31-54 and US 6,149,937 - column 1, lines 53-67). Because the instant ligand-based perfluorocarbon emulsion nanoparticle system can be considered to be a liposome (See US 5,656,287; column 4, line 27), the use of US 5,656,287 and US 6,149,937 to show where the lipophilic drug would have the propensity to

migrate is proper. Like the instant method of claim 1, the lipid-encapsulated particles (also referred to as liposome at column 4, line 27) are attached to a ligand-targeting moiety and may be used to target tissue surfaces (abstract and column 2, lines 54 - 56). Consistent with the instant specification, since microparticles comprising targeting ligand moieties would have the ability to bind to a cellular surface (including tissue) and remain stationary or "affixed," thereby interacting with the cell surface over an extended period of time, the examiner respectfully asserts that delivery of a drug or biological species would be inherently facilitated (page 7, lines 21-27 of the instant specification).

Response to Arguments

Applicant's arguments filed on 10/31/2006 have been fully considered but they are not persuasive. In response to the 06/27/2006 Non-Final Rejection, Applicant's assert that US 5,690,907, US 5,780,010, and US 5,958,371 do not anticipate the instant claim set. In making this assertion, the Applicants assert that the drugs set forth in US 5,690,907 are not inherently present in the lipid portion of the nanoparticles and that it is not a drug. The examiner respectfully disagrees with this assertion. As noted in the above rejection, biotinylated phosphatidylethanolamine is incorporated into the outer lipid monolayer of the perfluorocarbon emulsion nanoparticles disclosed in US 5,690,907 (Example 2; column 8, lines 66-67). As evidenced by US 4,595,680, phosphatidylethanolamine can be considered to be a drug, having activity against disorders related to the central nervous system (abstract). Thus, US 5,690,907 explicitly

teaches the incorporation of a drug, phosphatidylethanolamine, into the outer lipid layer of a perfluorocarbon emulsion nanoparticle. Additionally, US 5,690,907 also disclose combining the ligand-based perfluorocarbon emulsion nanoparticle system with chemotherapeutic agents or other drugs (column 7, lines 48-67). A specific example of the drugs set forth by US 5,690,907 is doxorubicin (column 7, line 54). Doxorubicin is a lipophilic drug that would have a tendency to incorporate into a lipid layer of a nanoparticle (See US 5,656,287 - column 2, lines 31-54 and US 6,149,937 - column 1, lines 53-67). Because the instant ligand-based perfluorocarbon emulsion nanoparticle system can be considered to be a liposome (See US 5,656,287; column 4, line 27), the use of US 5,656,287 and US 6,149,937 to show where the lipophilic drug would have the propensity to migrate is proper. As such, the examiner respectfully asserts that the above rejection is proper. It should be noted that, because there is no claim language indicating that the instant nanoparticles are hydrophobic (as discussed in the 1/26/2006 Remarks section), the nanoparticle of claim 1 is being viewed as a liposome-type formulation (also consistent with the description of the nanoparticle as a liposome in See US 5,656,287; column 4, line 27).

Claims 71-79, 82-93 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US 2001/0018072 ('072).

- '072 disclose solid porous matrix compositions and methods of using said compositions (abstract). According to '072, the solid porous matrix compositions are capable of delivering active agents to tissues and organs of individuals

(paragraphs 0002, 0048, 0280 - 0282). The compositions advanced by '072 may comprise a wide-variety of surfactants and active agents (abstract and paragraphs 0013, 0108, 0135).

- Like the instant application, the compositions disclosed by '072 may be in the form of nanoparticle vesicles with diameter from about 1 - 100 microns (paragraphs 0033, 0061, 0204, and 0277). The vesicles may comprise a lipid surfactant layer and a void (paragraph 0033). The lipid surfactant layer of the vesicles may comprise tocopherol or cholesterol (paragraph 0108). The void-like core of the vesicles may be filled with fluorocarbons, such as perfluorooctylbromide (paragraphs 0033 and 0121-0122). Additionally, the lipid-coated vesicles may also comprise a variety of different targeting ligands, from antibodies to amino acids (paragraph 0033 and 0048). As described by '072, the targeting ligand would "promote targeting of tissues." Since the targeting ligand promotes the interaction of the drug-based vesicle with a tissue, the examiner respectfully submits that the targeting ligand is "facilitating" the delivery of a drug to a ligand.
- As disclosed by '072, the biological agent may be combined with the drug in a variety of different ways (paragraph 0061). For example, in some embodiments, the biological agent can be incorporated into the vesicle or attached to the surface of the lipid (paragraph 0061). However, like the instant application, the biological agent can also be incorporated into the outer vesicle surface or stabilizing material (i.e. the lipid/surfactant portion of the vesicle - see page 6,

paragraph 0061, lines 28-44). According to '072, the limited association of a biological agent with the lipid portion of a vesicle advantageously allows said biological agent to migrate from the inner or outer surface of one microparticle to the surface of another microparticle (see page 6, paragraph 0061, lines 28-44). In terms of the biological agent suitable for use with the vesicle-based composition, '072 notes that a wide-range of drugs, from taxol, to dexmethasone, to beclomethasone dipropionate, to fentanyl citrate, to nifedipine may be used (paragraph 0135).

- The examiner respectfully asserts that '072 anticipates the instant claim set. Additionally, the examiner respectfully asserts that '072 provides motivation for one of ordinary skill in the art to formulate a tissue/organ targeting microparticle-based composition comprising a fluorocarbon core (or void liquid or gas) coated with a lipid layer and coupled to a targeting ligand, wherein a drug is incorporated in said lipid layer. Because '072 teaches the benefits of formulating a ligand-targeting vesicle/lipid composition wherein an active agent can be incorporated in the lipid portion of the composition, one of ordinary skill in the art would have been to formulate such a composition and use it to deliver active agents to a tissue or organ. Based on the teachings of '072, there is a reasonable expectation that a composition comprising a vesicle (with a fluorocarbon void or core) coated with a lipid and incorporating a drug into said lipid layer coating would be an effective drug delivery device, capable of delivering an active agent or drug to an organ or tissue. As such, it would have been obvious to one of

ordinary skill in the art at the time the invention was made, given the teachings of,'072, to formulate a composition comprising a vesicle (with a fluorocarbon void or core) coated with a lipid and a ligand targeting moiety and incorporating a drug into said lipid layer coating and use said composition to deliver active agents to the tissue or organ of a patent.

Response to Arguments

Applicant's arguments filed on 10/31/2006 have been fully considered but they are not persuasive. In response to the 06/27/2006 Non-Final Rejection, Applicant's assert that US 2001/0018072 do not anticipate or make obvious the instant claim set. In making this assertion, the Applicants assert that the disclosure of a 'solid' porous matrix set forth in US 2001/0018072 does not anticipate or render obvious the presently claimed invention. The examiner respectfully disagrees with this assertion. As noted in the above rejection, the same core fluorocarbon (such as perfluorooctylbromide) and lipid bilayer, since the fluorocarbon disclosed is the same as that used by applicant (shown in instant Example 1) it is therefore a liquid. Secondly, the phrase 'comprising' in instant claim 71 does not exclude the presence of solids. Furthermore, '072 teaches that the biological agent to migrate from the inner or outer surface of one microparticle to the surface of another microparticle (see page 6, paragraph 0061, lines 28-44), and as such it is present in the lipid layer. Applicant's own declaration has not shown that the drug is only present in the lipid layer, as all the ingredients are mixed together at

once (examples 1-2 and 4 instant specification), and as such US 2001/0018072 anticipates or makes obvious claims 71-79 and 82-93.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bethany Barham whose telephone number is (571)-272-6175. The examiner can normally be reached on Monday to Friday; 8:30 a.m. to 5:00 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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